



## mitochondrial trifunctional protein deficiency

Mitochondrial trifunctional protein deficiency is a rare condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting).

Signs and symptoms of mitochondrial trifunctional protein deficiency may begin during infancy or later in life. Features that occur during infancy include feeding difficulties, lack of energy (lethargy), low blood sugar (hypoglycemia), weak muscle tone (hypotonia), and liver problems. Infants with this disorder are also at high risk for serious heart problems, breathing difficulties, coma, and sudden death. Signs and symptoms of mitochondrial trifunctional protein deficiency that may begin after infancy include hypotonia, muscle pain, a breakdown of muscle tissue, and a loss of sensation in the extremities (peripheral neuropathy).

Problems related to mitochondrial trifunctional protein deficiency can be triggered by periods of fasting or by illnesses such as viral infections. This disorder is sometimes mistaken for Reye syndrome, a severe disorder that may develop in children while they appear to be recovering from viral infections such as chicken pox or flu. Most cases of Reye syndrome are associated with the use of aspirin during these viral infections.

### Frequency

Mitochondrial trifunctional protein deficiency is a rare disorder; its incidence is unknown.

### Genetic Changes

Mutations in the *HADHA* and *HADHB* genes cause mitochondrial trifunctional protein deficiency. These genes each provide instructions for making part of an enzyme complex called mitochondrial trifunctional protein. This enzyme complex functions in mitochondria, the energy-producing centers within cells. As the name suggests, mitochondrial trifunctional protein contains three enzymes that each perform a different function. This enzyme complex is required to break down (metabolize) a group of fats called long-chain fatty acids. Long-chain fatty acids are found in foods such as milk and certain oils. These fatty acids are stored in the body's fat tissues. Fatty acids are a major source of energy for the heart and muscles. During periods of fasting, fatty acids are also an important energy source for the liver and other tissues.

Mutations in the *HADHA* or *HADHB* genes that cause mitochondrial trifunctional protein deficiency disrupt all three functions of this enzyme complex. Without enough of this enzyme complex, long-chain fatty acids from food and body fat cannot be metabolized and processed. As a result, these fatty acids are not converted to energy, which can lead to some features of this disorder, such as lethargy and hypoglycemia. Long-chain fatty acids or partially metabolized fatty acids may also build up and damage the liver,

heart, and muscles. This abnormal buildup causes the other signs and symptoms of mitochondrial trifunctional protein deficiency.

## **Inheritance Pattern**

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## **Other Names for This Condition**

- MTP deficiency
- TFP deficiency
- TPA deficiency
- trifunctional protein deficiency, type 2

## **Diagnosis & Management**

### Formal Diagnostic Criteria

- ACT Sheet: Elevated C16-OH +/- C18:1-OH and Other Long Chain Acylcarnitines  
<https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/C16-OH.pdf>

### Genetic Testing

- Genetic Testing Registry: Mitochondrial trifunctional protein deficiency  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0342786/>

### Other Diagnosis and Management Resources

- Baby's First Test  
<http://www.babysfirsttest.org/newborn-screening/conditions/trifunctional-protein-deficiency>
- MedlinePlus Encyclopedia: Hypoglycemia  
<https://medlineplus.gov/ency/article/000386.htm>
- MedlinePlus Encyclopedia: Peripheral Neuropathy  
<https://medlineplus.gov/ency/article/000593.htm>

### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>

- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

## **Additional Information & Resources**

### MedlinePlus

- Encyclopedia: Hypoglycemia  
<https://medlineplus.gov/ency/article/000386.htm>
- Encyclopedia: Peripheral Neuropathy  
<https://medlineplus.gov/ency/article/000593.htm>
- Health Topic: Mitochondrial Diseases  
<https://medlineplus.gov/mitochondrialdiseases.html>
- Health Topic: Newborn Screening  
<https://medlineplus.gov/newbornscreening.html>

### Genetic and Rare Diseases Information Center

- Mitochondrial trifunctional protein deficiency  
<https://rarediseases.info.nih.gov/diseases/3684/mitochondrial-trifunctional-protein-deficiency>

### Educational Resources

- Illinois Department of Public Health  
<http://www.idph.state.il.us/HealthWellness/fs/mcad.htm>
- MalaCards: trifunctional protein deficiency  
[http://www.malacards.org/card/trifunctional\\_protein\\_deficiency](http://www.malacards.org/card/trifunctional_protein_deficiency)
- My46 Trait Profile  
<https://www.my46.org/trait-document?trait=Trifunctional%20protein%20deficiency&type=profile>
- Orphanet: Mitochondrial trifunctional protein deficiency  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=746](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=746)
- Screening, Technology, and Research in Genetics  
<http://www.newbornscreening.info/Parents/fattyacid disorders/TFP.html>
- Virginia Department of Health  
[http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet\\_TFP\\_English.pdf](http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_TFP_English.pdf)

### Patient Support and Advocacy Resources

- Children Living with Inherited Metabolic Diseases (CLIMB)  
<http://www.climb.org.uk>
- Children's Mitochondrial Disease Network (UK)  
<http://www.cmdn.org.uk/>
- FOD (Fatty Oxidation Disorders) Family Support Group  
<http://www.fodsupport.org/>
- United Mitochondrial Disease Foundation  
<http://www.umdf.org/>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22mitochondrial+trifunctional+protein+deficiency%22>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28mitochondrial+trifunctional+protein+deficiency%5BTIAB%5D%29+OR+%28TFP+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

### OMIM

- MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY  
<http://omim.org/entry/609015>

### **Sources for This Summary**

- Angdisen J, Moore VD, Cline JM, Payne RM, Ibdah JA. Mitochondrial trifunctional protein defects: molecular basis and novel therapeutic approaches. *Curr Drug Targets Immune Endocr Metabol Disord.* 2005 Mar;5(1):27-40. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/15777202>
- Boutron A, Acquaviva C, Vianey-Saban C, de Lonlay P, de Baulny HO, Guffon N, Dobbelaere D, Feillet F, Labarthe F, Lamireau D, Cano A, de Villemeur TB, Munnich A, Saudubray JM, Rabier D, Rigal O, Brivet M. Comprehensive cDNA study and quantitative analysis of mutant HADHA and HADHB transcripts in a French cohort of 52 patients with mitochondrial trifunctional protein deficiency. *Mol Genet Metab.* 2011 Aug;103(4):341-8. doi: 10.1016/j.ymgme.2011.04.006. Epub 2011 Apr 19.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21549624>
- Choi JH, Yoon HR, Kim GH, Park SJ, Shin YL, Yoo HW. Identification of novel mutations of the HADHA and HADHB genes in patients with mitochondrial trifunctional protein deficiency. *Int J Mol Med.* 2007 Jan;19(1):81-7.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/17143551>

- Gillingham MB, Purnell JQ, Jordan J, Stadler D, Haqq AM, Harding CO. Effects of higher dietary protein intake on energy balance and metabolic control in children with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency. *Mol Genet Metab.* 2007 Jan; 90(1):64-9. Epub 2006 Sep 22.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/16996288>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813195/>
- Oey NA, den Boer ME, Wijburg FA, Vekemans M, Augé J, Steiner C, Wanders RJ, Waterham HR, Ruiter JP, Attié-Bitach T. Long-chain fatty acid oxidation during early human development. *Pediatr Res.* 2005 Jun;57(6):755-9. Epub 2005 Apr 21.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/15845636>
- Sperk A, Mueller M, Spiekerkoetter U. Outcome in six patients with mitochondrial trifunctional protein disorders identified by newborn screening. *Mol Genet Metab.* 2010 Oct-Nov;101(2-3):205-7. doi: 10.1016/j.ymgme.2010.07.003. Epub 2010 Jul 24.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20659813>
- Spiekerkoetter U, Khuchua Z, Yue Z, Bennett MJ, Strauss AW. General mitochondrial trifunctional protein (TFP) deficiency as a result of either alpha- or beta-subunit mutations exhibits similar phenotypes because mutations in either subunit alter TFP complex expression and subunit turnover. *Pediatr Res.* 2004 Feb;55(2):190-6. Epub 2003 Nov 19.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/14630990>
- Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, Das A, Haase C, Hennermann JB, Karall D, de Klerk H, Knerr I, Koch HG, Plecko B, Röschinger W, Schwab KO, Scheible D, Wijburg FA, Zschocke J, Mayatepek E, Wendel U. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. *J Inherit Metab Dis.* 2009 Aug;32(4):488-97. doi: 10.1007/s10545-009-1125-9. Epub 2009 Apr 29.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/19399638>
- Spiekerkoetter U, Mueller M, Cloppenburg E, Motz R, Mayatepek E, Bueltmann B, Korenke C. Intrauterine cardiomyopathy and cardiac mitochondrial proliferation in mitochondrial trifunctional protein (TFP) deficiency. *Mol Genet Metab.* 2008 Aug;94(4):428-30. doi: 10.1016/j.ymgme.2008.04.002. Epub 2008 May 15.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/18485779>
- Spiekerkoetter U, Sun B, Khuchua Z, Bennett MJ, Strauss AW. Molecular and phenotypic heterogeneity in mitochondrial trifunctional protein deficiency due to beta-subunit mutations. *Hum Mutat.* 2003 Jun;21(6):598-607.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/12754706>
- Spiekerkoetter U, Khuchua Z, Yue Z, Strauss AW. The early-onset phenotype of mitochondrial trifunctional protein deficiency: a lethal disorder with multiple tissue involvement. *J Inherit Metab Dis.* 2004;27(2):294-6.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/15243991>
- den Boer ME, Dionisi-Vici C, Chakrapani A, van Thuijl AO, Wanders RJ, Wijburg FA. Mitochondrial trifunctional protein deficiency: a severe fatty acid oxidation disorder with cardiac and neurologic involvement. *J Pediatr.* 2003 Jun;142(6):684-9.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/12838198>

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